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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

re patent application of:

Stephen R. ASH

Serial No.: 09/143,143

Filed: August 28, 1998

METHOD FOR IRON DELIVERY TO A PATIENT BY TRANSFER FROM DIALYSATE

Before the Examiner
J. Pak

Group Art Unit 1616

May 16, 2002

DECLARATION UNDER 37 C.F.R. §1.132

Honorable Assistant Commissioner
For Patents
Washington, D.C. 20231

Sir:

I, Stephen R. Ash, M.D., hereby declare that:

1. I am the inventor on the above-captioned patent application and am familiar with its content.

2. My degrees include a B.A. degree in Physics from Northwestern University and a M.D. in Medicine from Kansas University Medical School. I have significant experience in research relating to all areas of blood treatment. I have authored and co-authored hundreds of publications, published abstracts, book chapters, and review articles and I am the inventor or a co-inventor on more than thirty U.S. patents and patent applications in the field of the present invention. I have also made numerous seminar presentations and have been awarded a number of grants and honors in the field of the present invention. Further information relating to my education and experience in this field is provided in my *curriculum vitae*, a copy of which is attached hereto.

3. I have reviewed the Office Action dated November 16, 2001. In this regard, I have considered the conclusion in the Action that claims 24-29, 31-37, 39-41, 44

and 46-66 are rejected under 35 U.S.C. 103(a) as being "unpatentable over the combined teachings of Bellini et al. in view of the acknowledged prior art and Martindale The Extra Pharmacopoeia for the reasons first fully set forth in the Office Action of Paper No. 11." In the present Office Action, the Examiner summarizes the ground of rejection as follows:

> Bellini et al. clearly disclose concentrated and diluted peritoneal dialysis solutions that contain electrolytes, gluconate salts such as iron gluconate and glucose and the ordinary skilled artisan has been taught that iron dextran can be administered intraperitoneally. The ordinary skilled artisan in this field is a highly educated and trained medical professional responsible for critical care of dialysis patients, who would not blindly formulate dialysis solution ingredients to induce a toxic reaction. Upon having been taught that iron gluconate and iron dextran may be given to dialysis patients by the intraperitoneal route, it would have been through routine experimentation that he/she would have arrived at the appropriate concentrations of electrolytes and iron gluconate or iron dextran (with a molecular weight of less than 50,000) suitable for a dialysis patient in need of iron supplementation as claimed.

(Office Action, Page 3). Based upon my training and experience in this field, I disagree with the Examiner's assertion and conclusions. The references cited by the Examiner would not motivate someone skilled in this field to practice the present invention for the reasons discussed below.

4. With respect to the Examiner's assertion that "the ordinary skilled artisan has been taught that iron dextran can be administered intraperitoneally," it is important to recognize that the iron dextran compositions to which the Examiner refers do not fall within the scope of the pending claims. Each of the pending claims includes a recitation of "an iron complex dissolved in the water, the complex ... having a molecular weight of less than about 50,000." Iron dextran compositions identified by the Examiner are suspensions of macromolecules that include multiple dextran molecules and iron tightly bound in the form of macromolecules having molecular weights of about 350,000. Such macromolecules are discussed in the present application in the paragraph spanning pages 21 and 22, wherein they are referred to as "secondary complexes" and are clearly distinguished from the present invention.

5. The present application also emphasizes the reason that macromolecules such as iron dextran have been historically selected for use as a vehicle for intramuscular and intravascular iron delivery. Namely, because iron dextrans are tightly formed, non-

soluble macromolecules in aqueous suspension, and thus do not readily release iron into the blood, medical providers in this field have considered them to be the only safe vehicles for parenteral iron delivery. Indeed, great efforts have been consistently made in the prior art to ensure that soluble iron was not contacted with blood due to the widespread belief that free iron is toxic. As stated at page 7 of the present application, "it is widely believed that soluble iron complexes are unacceptable iron delivery agents, this belief being based upon a fear of the toxicity of free iron in blood." (Specification, page 7, lines 5-8). This widespread belief is described in the specification and reiterated throughout the record of this case. It is also shown in recent publications, such as, for example, Gupta, A., Crumbliss, A., Treatment of iron deficiency anemia: are monomeric iron compounds suitable for parenteral administration? J Lab Clin Med. 2000 Nov; 136(5):371-378 . In this article, the authors state that: "Simple iron salts such as chloride, sulfate and ascorbate are considered too toxic for parenteral administration, because dissolution of these compounds liberates free iron." This statement and subsequent statements regarding the toxic activity of free iron are supported in the article with eight references to journal articles published from 1950 to 1999.

6. In view of the above, it is clear that: (1) a reference describing inclusion of iron dextran in a dialysate does not read on the presently-pending claims, which recite "an iron complex dissolved in the water, the complex ... having a molecular weight of less than about 50,000," and (2) a reference describing inclusion of iron dextran in a dialysate would not motivate a person of ordinary skill in the art to select a low molecular weight iron complex (referred to in the present specification as a "primary complex") for inclusion in a dialysate composition.

7. With respect to the Bellini et al. reference, it is again important to acknowledge the widespread and generally accepted belief that soluble iron, or free iron, induces a toxic reaction when contacted with blood in any form other than a tightly-bound, non-soluble macromolecule such as iron dextran. When reading the Bellini et al. reference against this background of information, it is clear that Bellini et al. did not contemplate, nor did they intend to suggest, that it would be desirable to deliver iron to a patient via peritoneal dialysis in the form of iron gluconate. Indeed, such a suggestion is so

contradictory to the generally held belief that such a suggestion would have been immediately discredited by a person of ordinary skill in the art as a simple error unless it were accompanied by a full description, including examples of test results, showing that such a composition of soluble iron is not toxic. The absence of any such information in the Bellini et al. reference supports the conclusion that Bellini et al. did not contemplate, teach or suggest delivery of iron to a patient via dialysate or inclusion of iron gluconate in a dialysate composition.

8. Indeed, the Bellini et al. reference is not directed to iron delivery technology, but is rather directed to providing alternative osmotic substances other than glucose for inclusion in peritoneal dialysates. In this regard, Bellini et al. discloses "solutions for peritoneal dialysis that contain an osmotic substance which is an alternative to glucose." (Col. 1, lines 1-3). More specifically, Bellini et al. disclose "a peritoneal dialysis solution ...characterized in that it comprises an osmotic substance chosen among gluconic acid and its pharmaceutically acceptable salts." (Col. 2, lines 30-34). Furthermore, the concentration of a gluconic acid and/or salt in a peritoneal dialysis solution is described in Bellini et al. in functional terms of providing a final osmolarity of between 200 and 500 mOsm/l. (Col. 2, lines 43-47).

9. The Bellini et al. reference includes a list of gluconic acid salts, including calcium gluconate, zinc gluconate, sodium gluconate, sodium stibogluconate, magnesium gluconate and iron gluconate (Col. 2, line57 through Col. 3, line 1). However, this list would be considered by a person of ordinary skill in this art to be a generic list of sources of gluconic acid. No example is provided in this reference of any experiment in which iron gluconate was included in a peritoneal dialysate, and a person of ordinary skill in the art would not have been motivated to select iron gluconate for such use in view of the widespread fear of iron toxicity. A person or ordinary skill in the art would have concluded that iron gluconate was simply included in this list in error, without consideration of the negative physiologic effect that it would have been believed to cause. Therefore, Bellini et al. does not teach, suggest or enable a peritoneal dialysis protocol using a dialysate including iron gluconate, and it would not motivate a person of ordinary skill in the art to include iron gluconate in a dialysate.

10. Combined with the above, Bellini et al. states that: "Advantageously, gluconic acid and/or any salts thereof are included in the peritoneal dialysis solution according to the present invention at a concentration of 1 to 5% by weight and therefore of 10 g/l up to 50 g/l." (Col. 2, lines 38-42). If iron gluconate were selected as the gluconic acid salt in Bellini et al., the dialysate would include from 10 g/l up to 50 g/l of iron gluconate, which would equal from about 91,000 to about 455,000 μg/dl of soluble free iron in the peritoneal dialysate. By comparison, the concentration of iron that is tightly bound to plasma proteins in the blood is from 40-135 μg/dl. While this dialysate may have good osmotic properties by virtue of a gluconic acid salt, a person of ordinary skill in the art would dismiss any notion of including iron gluconate as the source of the gluconate salt, concluding that a peritoneal dialysate including iron gluconate, especially from about 91,000 to about 455,000 μg/dl of iron from iron gluconate, would transfer huge amounts of iron to the blood and would therefore be toxic. The lower end of Bellini's range is a concentration of iron that is more than 300 times greater than the iron concentrations in dialysate concentrates described and claimed in the present application.

11. Furthermore, Bellini et al. would not motivate a person of ordinary skill in the art to include even a small amount of iron gluconate due to the belief that the iron gluconate would have a detrimental impact on the patient's blood. No suggestion or motivation exists in Bellini et al. or any other prior art of record to make or use a dialysate including an iron complex "having a concentration in the water to provide an iron concentration of from about 1 to about 250 μg/dl" or a dialysate concentrate including electrolytes and an iron complex with "concentrations in the water whereby the composition is effective for dilution to provide a dialysate having ... an iron concentration of from about 1 to about 250 μg/dl" as recited in the pending claims. A skilled artisan would not "through routine experimentation...have arrived at the appropriate concentrations of...iron gluconate...suitable for a dialysis patient in need of iron supplementation" as asserted by the Examiner because a skilled artisan simply would not have selected iron gluconate for use in this manner in the first instance.

12. The undersigned agrees with the Examiner's assertion that, "The ordinary skilled artisan in this field is a highly educated and trained medical professional

responsible for critical care of dialysis patients, who would not blindly formulate dialysis solution ingredients to induce a toxic reaction." Indeed, for this very reason, an ordinary skilled artisan in this field prior to the present invention would not have incorporated an iron complex having a molecular weight of less than about 50,000 into a dialysate because this education and training would have included significant information regarding the widespread belief that such an ingredient would cause a toxic reaction. I agree that an ordinary skilled artisan would not blindly include an ingredient believed to induce a toxic reaction and therefore prior to the present invention, such an artisan would not have included an iron complex as recited in the pending claims in a dialysate composition.

13. In summary, in view of my experience and training in this field, I disagree that the references cited by the Examiner would motivate a person of ordinary skill in the art to practice the present invention or that the references make the invention obvious. This conclusion is based upon the following facts: (1) information regarding the inclusion of iron dextran in a dialysate would not motivate a skilled artisan to include an iron complex as recited in the pending claims in a dialysate; and (2) Bellini et al. does not teach, and would not motivate a skilled artisan to make or use, a dialysate composition including iron gluconate.

14. I further declare that all statements made herein are of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the application or any patent issued thereon.

May 16, 2002
Date

Stephen R. Ash, M.D.